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CLINICAL CURIOSITY

BIPOLAR DISORDERS WILEY

First manic episode following COVID-19 infection

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1 | CASE PRESENTATION

A 56-year-old Caucasian male with no past psychiatric history presented to the emergency department (ED) for evaluation of new onset (24 h) odd and erratic behavior preceded by a 4-week period of decreased need for sleep, averaging 2 h per night. The sleep pattern change began within 1 week of an untreated symptomatic upper respiratory infection suspected to be due to COVID-19. On presentation to the ED, he endorsed fluctuating mood, increased energy, distractibility, and overvalued religious ideation that he was a prophet, although this was not a fixed belief. He was conceptually disorganized, responded to religiously themed command auditory hallucinations, but demonstrated fair insight into his unusual behavior. Family and personal past psychiatric history both were unremarkable. Medical workup in the ED included head computed tomography, general laboratory studies, and SARS-Coronavirus-2 RNS testing; other than mild neutrophilia and thrombocytosis, all studies were negative. He was admitted to the medical service for further evaluation. Risperidone 1 mg daily for psychotic symptoms and lorazepam 1 mg at bedtime for sleep were initiated.

Additional inpatient medical workup included brain magnetic resonance imaging, which was negative for any enhancing lesions or signs of encephalitis. Screening for autoimmune disorders, heavy metals, drug use, HIV, and sexually transmitted disease testing was negative. SARS-CoV-2 nucleocapsid total antibody was positive. This antibody, with an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) with neutrophilia and thrombocytosis, was suggestive of an acute inflammatory state and recent COVID-19 infection. He did not receive COVID-19 vaccination. His symptoms rapidly improved following 24 h of hospitalization. Given such rapid response, a diagnosis of brief psychotic disorder was made, and he was discharged home with no follow-up medications.

Ten days post hospital discharge, he re-presented to the ED with labile mood, increased energy, pressured speech, talkativeness, distractibility, overvalued religious thought, and brain fog. This was a classic manic episode of elevated mood and energy. Given his previous positive response to medications, risperidone 1 mg was re-started with scheduled outpatient follow-up. One week later, at outpatient psychiatric follow-up, risperidone was further increased to 2 mg due to continuation of hyperactivity though his sleep had improved to 7 h per night.

2 | DISCUSSION

To our knowledge, this is the first observation of a manic episode with psychosis following a suspected mild symptomatic COVID-19 infection in a patient not treated with corticosteroids or antibiotics. Given the negative past psychiatric history and the relatively uncommon first episode age of onset, we hypothesize this manic episode is related to prior COVID-19 infection. This is further supported by the elevation in ESR and CRP in an otherwise healthy patient and appears consistent with a COVID-19-associated manic episode. Unlike the typical characteristics of older age bipolar disorder, defined as individuals over 50 years old, this case has no risk factors for cerebrovascular disease or structural brain abnormalities including stroke, tumor, or white matter hyperintensities.

This patient was initially diagnosed with brief psychotic disorder based on the predominant psychotic presentation in the ED. However, after further longitudinal observation in the outpatient setting, the case was finally diagnosed as a manic episode with psychotic features. The progression of hypomania to psychotic mania can vary significantly between individuals. The lack of continuation therapy after the initial remission led to the relapse of mania. In line with evidence-based treatment for mania, this patient likely would

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have benefited with continued treatment with an antipsychotic mood stabilizer.

There is one case report of manic-like symptoms in the setting of COVID-19 infection in China.[1] As in our case, they also report new manic-like symptoms in a patient with no previous psychiatric history. There was rapid reduction in manic symptoms after initiation of antipsychotic treatment; as the authors noted, the patient had received high-dose methylprednisolone for treatment of symptomatic COVID-19 infection, which is known to precipitate mood episodes.[2] There are also two case reports of psychotic depression following COVID-19 infection, one in the case of concurrent azithromycin nitrofurantoin treatment, and the other with progressive symptoms of anxiety and psychosis symptoms.[3] Given the clear delineated timeline (Figure 1), as well as symptoms meeting the criteria of manic episode, our case could further contribute to our understanding of a variety of neuropsychiatric presentations following symptomatic COVID-19 infections.

Viral infections (i.e., influenza, coronavirus, cytomegalovirus, and herpesvirus) with secondary immune activation are increasingly recognized as an etiologic factor in the pathogenesis of bipolar disorder.[4] It is not certain whether this case may be correlated with SARS-Coronavirus-2 itself or may be related to the immune response evidenced by an increased CRP and thrombocytosis. These viruses have neurotropic characteristics which could penetrate blood–brain barriers, as well as stimulate the production of cytokines such as tumor necrosis factor-α, interleukins 1 and 6, and interferon-α, causing systemic symptoms. However, it is increasingly recognized that a multisystem inflammatory gene–environment interaction is likely contributing to the risk of illness onset.[5]

This case's time interval between the onset of respiratory symptoms and the emergence of the manic episode falls into the

Key Message

The hypothesis has been suggested that viral infections are related to the pathogenesis of bipolar disorder. COVID-19 infection could trigger an initial manic episode, which rapidly improves following treatment with atypical antipsychotics. Prolonged treatment needs to be considered even after the early remission as with typical manic episodes. Maintenance treatment for mood stabilization should be considered and further investigated if there are differential pharmacological outcomes compared with typical manic episodes.

Learning Points

- Manic or hypomanic episodes can present following a symptomatic COVID-19 infection even in a previously naïve patient.
- The antipsychotics which have been effective for manic episodes seem to be effective for a manic episode occurring in relation to COVID-19 infection as well regardless of the medical treatment provided for the COVID-19 infection.

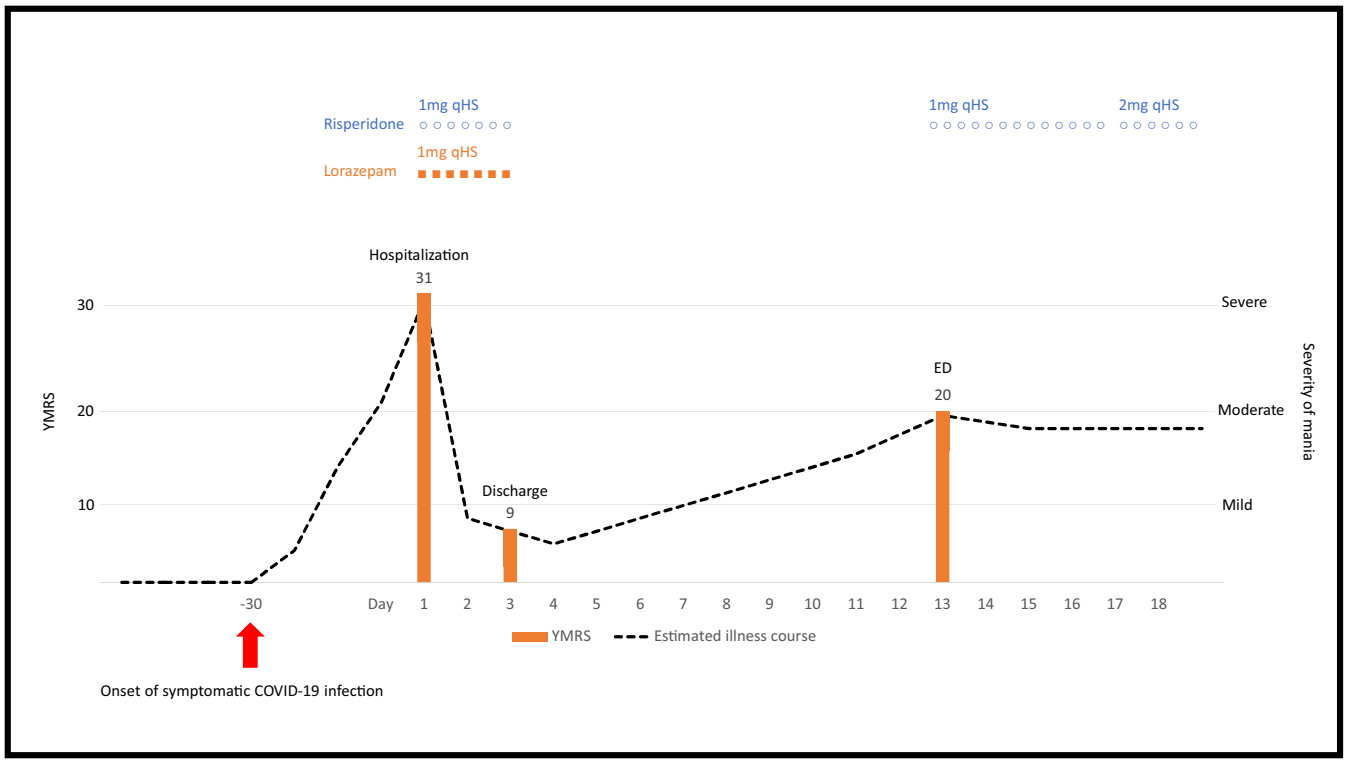

FIGURE 1 Prospective life chart of mania

post-illness stage similar to the viral prodrome ahead of anti-N-methyl-D-aspartate receptor encephalitis. Given that the patient's psychiatric symptoms were limited to the manic episode with psychotic features with a prompt response to known medications for acute manic episodes, this case shed light on a part of the hypothesis. Further studies in a more molecular approach including genomics are needed to better understand disease pathogenesis.

This case report has limitations in several respects. First, we cannot confirm the causality between COVID-19 infection and the emergent manic episode. However, we can speculate the association between the infection associated with elevation of ESR and CRP and the abrupt onset of manic symptoms. Second, it is not fully known when the patient was infected with SARS-Coronavirus-2 as he did not undergo a PCR test at the time of acute respiratory symptoms, though antibody testing was positive within 4 weeks of symptom onset suggesting a recent infection. Third, cerebrospinal fluid was not obtained to test for SARS-Coronavirus-2 antibody or antigen. However, given the lack of typical meningitis signs including no fever or nuchal rigidity, and given the response to treatment with antipsychotic and benzodiazepine, this testing was not completed. Finally, the natural course of this case has not been fully followed up yet.

In conclusion, we report a case of a first-onset manic episode with psychosis in a 56-year-old male after a presumed symptomatic COVID-19 infection, based on positive SARS-CoV-2 nucleocapsid total antibodies, in a psychiatric-naïve patient with no family history of bipolar affective disorder and no additional risk factors. Clinicians need to be aware that an initial manic episode can present in the setting of the recent COVID-19 infection. It is likely that the patient would benefit from treatment based on the current guideline for acute mania, as well as maintenance treatment for mood stabilization. Future research related to viral infections and the immune response-related hypothesis in bipolar affective disorders is needed to better understand the pathogenesis in our field.

AUTHORS' CONTRIBUTION

JP and MK participated in the treatment of the case, wrote the initial draft and revised it, interpreted the case, and conceptualized the work. MGR, NAN, and AA revised the work and interpreted the case. MAF revised and finalized the draft, interpreted the case, and conceptualized the work.

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